



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kai LICHIA et al.

Examiner: KOSAR, Andrew D.

Serial No.: 10/762,582

Group Art Unit: 1654

Filed: January 23, 2004

Title: HYDROPHILIC, THIOL-REACTIVE CYANINE DYES AND CONJUGATES
THEREOF WITH BIOMOLECULES FOR FLUORESCENCE DIAGNOSIS

APPEAL BRIEF

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on November 28, 2006, please consider the following.

Applicants request that the Appeal Brief Fee of \$500.00 paid on March 28, 2007, be applied to the present Appeal Brief. There is a \$10.00 difference between the previous Appeal Brief Fee and the current Appeal Brief Fee.

The Commissioner is hereby authorized to charge any fees associated with this response, including the above-discussed \$ 10.00, or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The real party in interest is Schering AG.

(ii) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

01/29/2008 SZEWDI1
03/29/2007 AWONDAF1 00000046 10762582
02 FC:1402 -500.00 OP

(iii) STATUS OF CLAIMS

Claims 1-25, 33 and 35-41 are pending in the present application.

Claims 26-32 and 34 were cancelled.

02 FC:1402

510.00 OP

Claims 2, 3, 5, 8, 11, 14-17, 20-25, 33 and 36-39 were withdrawn from consideration.

Claims 6, 7, 9, 10, 12, 13 and 40 were allowed.

Claims 1, 4, 18, 19, 35 and 41 were rejected.

Claims 1, 4, 18, 19, 35 and 41 are on appeal.

(iv) STATUS OF AMENDMENTS

No amendment was filed after the Office Action of September 26, 2007.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' appealed invention is directed to indotricarbocyanine dyes of formula (I), see structure thereof in claim 1, for example, (see page 4, last paragraph on said page, to about the last 6 lines of page 5, of the specification), and to solvates thereof (see page 5, line 7 from the bottom of the page, of the specification).

The appealed invention is furthermore directed to solvates of to indotricarbocyanine dyes of formulae II, III, V, VI, VIII and IX, see structures thereof in claim 40, for example, (see pages 8-10 and page 5, line 7 from the bottom of the page, of the specification).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejections are:

- (1) the rejection under 35 U.S.C. § 103, i.e., whether claims 1, 4, 18 and 19 are unpatentable over Zaheer in view of Chorev or Rosenblatt;
- (2) the rejections under 35 U.S.C. § 112, first paragraph, i.e., whether claims 35 and 41 are enabled; and
- (3) the rejections under 35 U.S.C. § 112, first paragraph, i.e., whether claims 35 and 41 comply with the written description requirement.

(vii) ARGUMENT

The Rejections Under 35 USC 103:

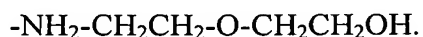
The rejection is set out in the Final Rejection mailed on July 28, 2006, the Office Action mailed on December 30, 2005, and the Office Action mailed on July 26, 2007.

The rejection was originally over the combination of eight (8) references, with the combination in the latest Office Action being down to three (3) references, where the Office Action takes parts of various compounds, e.g., certain groups present in various compounds,

from different references, and combines them, e.g., places them on compounds of other reference(s), to yield applicant's claimed compounds. The rejection in essence did not change over the course of the above mentioned Office Actions, but merely in the last Office Action, the number of references combined was lowered.

Such combination of various parts of different compounds is not a proper basis for an obviousness rejection under strong Federal Circuit precedent such as *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) and *In re Baird*, 16 F.2d 380, 29 U.S.P.Q. 2d 1550 (Fed. Cir. 1994).

Note in this regard, particularly, the analysis used by the Court in *Jones*. The group at issue in *Jones* had the structure



The PTO tried to rely on the single reference's compound having two $\text{CH}_2\text{CH}_2\text{OH}$ groups attached to a single N atom, instead of linked together as shown above. The Court stated that one could not ignore the fact that the two $\text{CH}_2\text{CH}_2\text{OH}$ groups were not joined together to form the ether linkage-containing group required in the claim. One could not simply rely on the " $-\text{CH}_2\text{CH}_2\text{O}-$ " features of the reference; one had to consider the entirety of the structure involved. The Patent and Trademark Office also tried to rely on a morpholino group in the single reference wherein the nitrogen atom has two ethyl groups bonded to it and linked to each other by a single oxygen atom, thereby allegedly providing the "missing" ether oxygen noted above. Again, the Court stated that one could not ignore the entirety of the structure, i.e., the fact that this prior art group compound was cyclic. One could not apply components of its structural features in isolation apart from the group's overall structure. Other similar analyses were rejected by the Court.

Likewise here to the situation in *Jones*, the disclosure of Chorev, for example, that the compounds therein have a maleimido moiety which have a high specificity towards a sulfhydryl group cannot be separated from the specific compounds taught by Chorev. Such piecing together of a chemical invention's compound from various differing structures from different references is improper under well settled precedents. For example, nothing in Chorev teaches where, for example, sulfonic acid groups of the other cited references should be placed, or how such combination could be achieved.

Moreover, it is entirely unclear from the references that even if such piecing together would be performed, whether the resultant compounds would have the desired properties.

One of ordinary skill in the art would not have an expectation of success based on the teachings of the prior art to prepare compounds with the desired properties.

Disclosure of particular generic formulae and/or species with their particular set of structural components, under *Baird* and *Jones*, does not motivate or provide adequate reason to one of ordinary skill in the art to select various structural features from different compounds or from different generic formulae in isolation and apply them to other compounds or other generic formulae.

Moreover, without appellants' own disclosure as a roadmap to piecing together the claimed invention herein, one of ordinary skill in the art would not have ended up with appellants' invention based on the disclosure of the various references. Not one single reference generically teaches each and every component of the claimed invention herein and/or even how the pieces of the various compounds should be formulated into a single structure.

Additionally, there is no reason provided in the references for the particular combinations alleged. For example, the compounds have differing uses. The compounds of Zaheer are IRDye78 Conjugates for Near-Infrared Fluorescence Imaging (see title) and the compounds of Chorev are Thiol-Reactive Maleimido-Based Radiolabeling Reagents (see title). Both the uses of the compounds of the references are different, and the structures of the disclosed compounds are not similar. Without the disclosure of the present application, one of ordinary skill in the art would not know how pieces of the compounds of these references should be pieced together. Moreover, Chorev would not even be considered because it is non-analogous art, relating to a different field and problem.

There is no reasoning justifiable under controlling precedent that would allow the holding of obviousness of a compound based on the piecing together of said compound from various unrelated compounds of different references.

In the final Rejection mailed on July 28, 2006 the Examiner distinguishes the present case from *Jones*, and states that

Jones compares two compounds ... and the issue is connectivity of atoms within a single structure, and the non-obviousness to rearrange the atoms, and not the reliance upon secondary references to bring in the missing elements. Here the compounds of the prior art are highly analogous, sharing a significant core structure, where any one reference could be relied upon as the primary reference.

See also the comment to the same end in the Office Action mailed on July 26, 2007.

Applicants submit that the inspiration to “rearrange” elements or groups within a single compound, which was not allowed to stand in support of an obviousness rejection in *Jones*, would more likely occur to one of ordinary skill in the art than the selection of elements or various groups from various references, e.g., 8 references, and rearrange such elements or groups to achieve a specific structure. For example, one of ordinary skill in the art would not first have to find a reason to select the various references from among many prior art references, as one reference would contain all that is needed to make selections for the rearrangement.

Additionally, the allegation that the compounds combined share a significant core structure is incorrect. A comparison of the structures of the compounds of the references readily illustrates the lack of a common significant core structure. The compounds of Chorev contain two single cyclic groups, one being a single phenyl ring with a hydroxy group attached and an R² group which is a radionuclide, e.g., ¹²²I, ⁷⁷Br, etc., (see claim 1 of Chorev, for example) and this phenyl ring is connected by a bridging group to a second single cyclic group. The compounds of, e.g., Zaheer, see, page 357, contain two polycyclic groups, to which various substituents are attached, e.g., SO₃ and methyl groups, and these two polycyclic groups are connected by various linking groups, which include further cyclic groups, etc.

Neither cyclic group in Chorev’s compounds even remotely resembles the polycyclic groups in Zaheer’s compounds. Additionally, the respective bridging groups of these references also do not appear to overlap in structure. Thus, the allegation that the compounds of the various references share a significant core structure is incorrect. These compounds have nothing in common other than that they are both compounds made up of various atoms, e.g., carbon, nitrogen, etc.

For all the foregoing reasons, the claims are not obvious.

The Enablement Rejections Under 35 USC 112:

The Final Rejection mailed on July 28, 2006 and the Office Action mailed on July 26, 2007, cite Vipagunta teaching allegedly that generally the prediction of the formation of solvates is complex and difficult, and that the result may be an unstable system, that various types of phase changes are possible, and that such may affect bioavailability, etc. Based on such teachings, the Final Rejection alleges that the art has high unpredictability with regards to solvates and that one would be burdened with undue experimentation to make solvates.

Even assuming that all the general allegations regarding the teachings of Vipagunta are correct, there is no basis for the rejection.

First and foremost, a specification disclosure which “contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra*.

The Examiner has not established any basis to doubt objective enablement. There is no indication that one of ordinary skill in the art would have questioned that solvates could be formed in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005).

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. “The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation.” *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take various compounds of the invention, which are enabled, bring them together with various solvents under various conditions and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Any amount of instability, phase changes, etc., can be determined by routine testing. As discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the “test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine.”

The Examiner also alleges that the bioavailability of the solvates may be different than those of the compounds themselves. However, such has no relation to whether such solvates are enabled or not.

The Written Description Rejections Under 35 USC 112:

The Office Action mailed on July 26, 2007, alleges that solvates of the claimed compounds lack written description. The reasoning provided is similar to the reasoning provided in the enablement rejection. Thus, the discussion from above is incorporated herein by reference.

The specification on page 5 recites solvates of the claimed compounds, but does not provide examples of solvates, e.g., by examples of preparation.

A recent decision regarding written description is highly relevant to the present situation, i.e., *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006). In *Falkner* the invention related to “a way of making vaccines safer by deleting or inactivating an *essential*, rather than an inessential, gene from the viral vector's genome.” The approach was taught to be applicable to many different kinds of vector viruses. Detailed description of only the herpes virus was present in the specification, with pox virus being mentioned. The specification did not identify any *essential* genes in pox virus or describe the inactivation of such *essential* genes. Moreover, the specification specifically admitted that vaccines were not produced with pox virus. The claimed invention was however directed to the making of a vaccine with a pox virus. A written description rejection followed. The Federal Circuit decided that:

[W]e hold, in accordance with our prior case law, that (1) **examples are not necessary to support the adequacy of a written description** (2) the **written description standard may be met** (as it is here) **even where actual reduction to practice of an invention is absent**; and (3) **there is no per se rule that an adequate written description of an invention** that involves a biological macromolecule **must contain a recitation of known structure**. (Emphasis added.)

Thus, even absent specific examples of solvates, or detailed description of the structures thereof, or even absence of actual reduction to practice of solvates, in view of *Falkner*, there is not an adequate reason provided by the Office Action for the alleged lack or written description rejection. Applicants teach in the application that the invention includes the solvates of the claimed compounds, and those of ordinary skill in the art do not have any reason to conclude that the inventors have not invented the claimed invention or were not in possession of the claimed invention at the time of the filing of the present application.

Reversal of the rejections is respectfully and courteously requested.

Respectfully submitted,

/Csaba Henter/

Csaba Henter (Reg. No. P-50,908)
Anthony J. Zelano (Reg. No. 27,969)
Attorneys for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

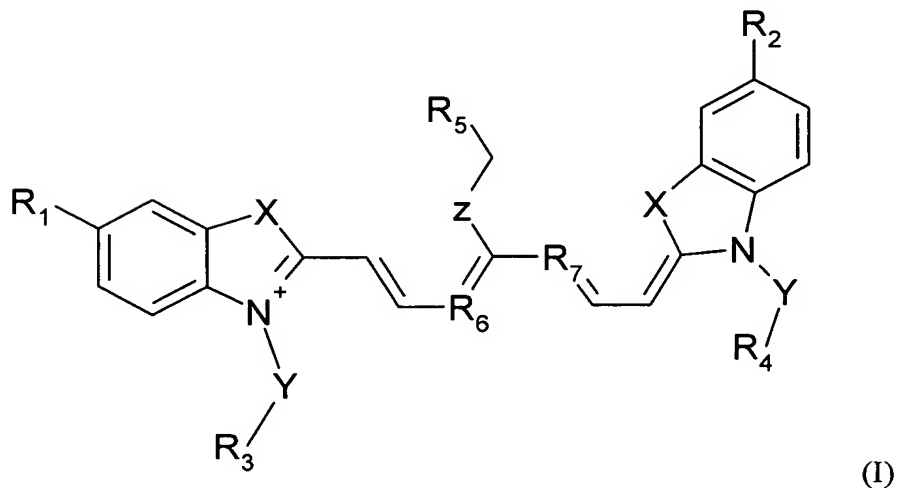
Attorney Docket No.: SCH-2208

Date: **January 28, 2008**

CH/AJZ/pdrK:\Sch\2000 to 2999\2208\Appeal Brief No 2.doc

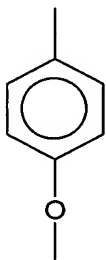
(viii) CLAIMS APPENDIX

1. An indotricarbocyanine dye of formula (I),



in which

- X is O, S or C, wherein, when X is C, it is substituted twice by methyl, ethyl, propyl, isopropyl and/or butyl,
- Y is CH₂-CH₂ or CH₂-CH₂-CH₂,
- Z is C₁ to C₅ alkyl, wherein one or more C atoms are optionally replaced by O or S, or is



which is bound by an ethylene or a methylene bridge to

R₅,

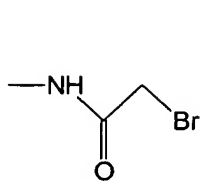
R₁ to R₄ are, independently of one another, SO₃H or H, with the proviso that at least three of R₁ to R₄ are SO₃H,

R₅ is COOH, NH₂, -CO-NH-R₈-R₉, -NH-CS-NH-R₈-R₉ or -NH-CO-R₈-R₉,
in which R₈ is an unbranched C₂-C₁₃ alkyl, in which C atoms are optionally

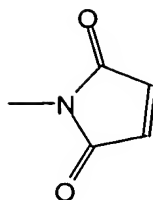
replaced by O or S,

R₉

is



or



or chloroacetyl,

bromoacetyl, iodoacetyl, chloroacetamido, iodoacetamido, chloroalkyl,

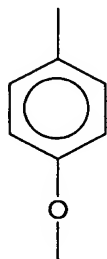
bromoalkyl, iodoalkyl, pyridyl disulfide or vinyl sulfonamide,

R₆ and R₇ are CH or are connected together by a C₃-alkylene group to form a cyclohexyl, which optionally can be substituted in para-position with a C₁ to C₄-alkyl radical,

or a salt thereof.

4. An indotricarbocyanine dye according to claim 1, in which

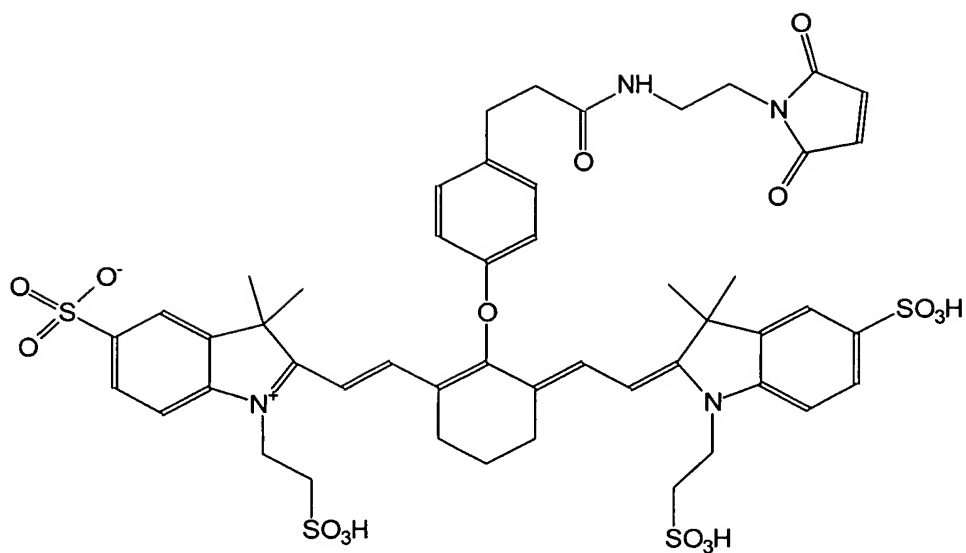
Z is



which is bound by an ethylene or a methylene bridge to R₅,

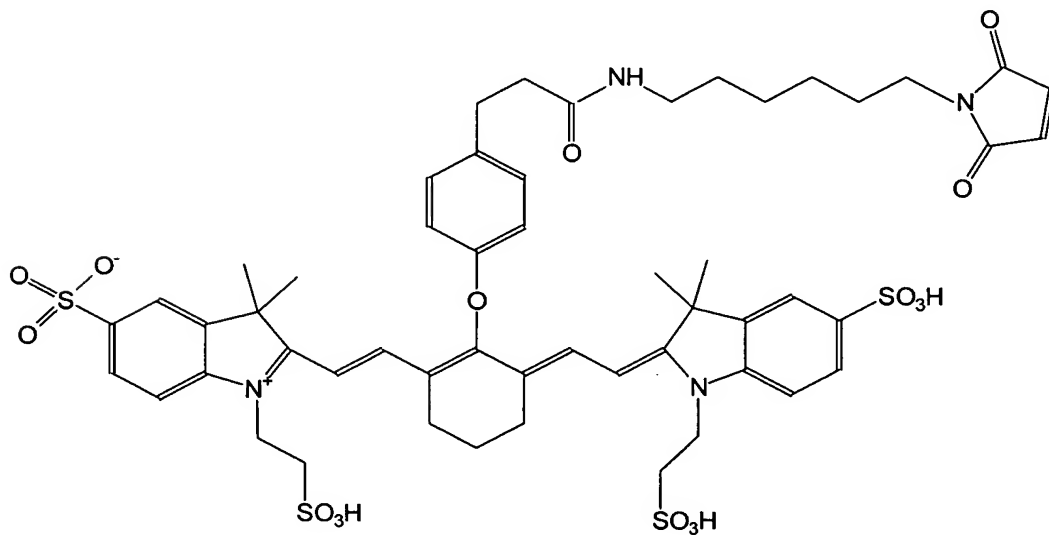
and R₆ and R₇ are connected together by a C₃-alkylene group to form a cyclohexyl.

18. An indotricarbocyanine dye according to claim 4 of formula (XIV)



or a salt thereof.

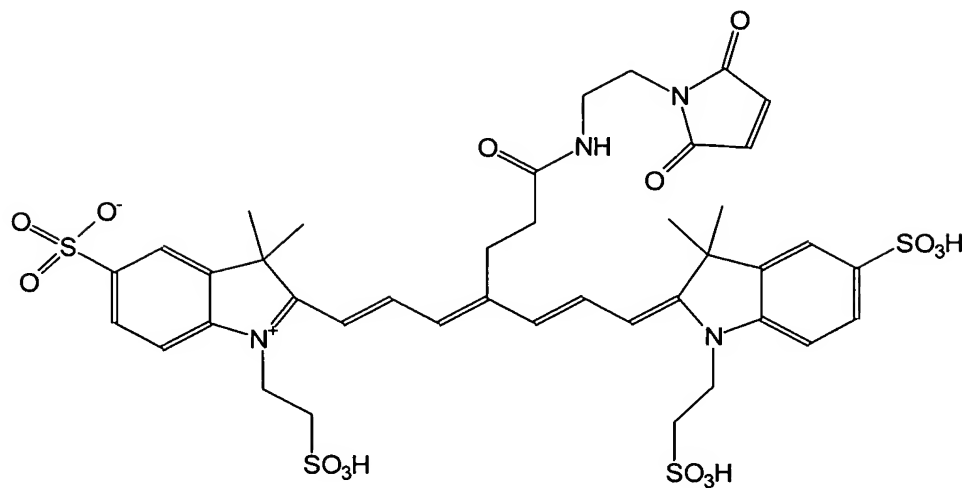
19. An indotricarbocyanine dye according to claim 4 of formula (XV)



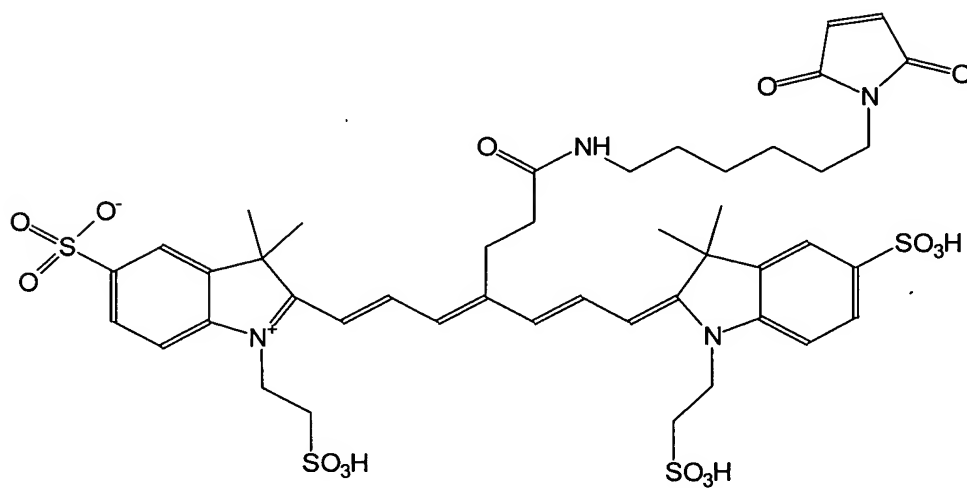
or a salt thereof.

35. A solvate of a compound of claim 1, which comprises a compound of formula I in combination with a solvent molecule.

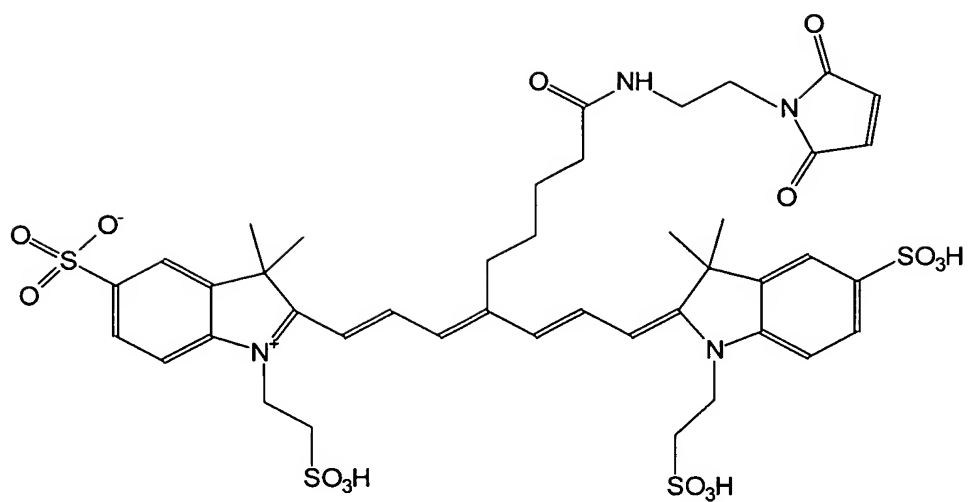
40. An indotricarbocyanine dye of formula (II)



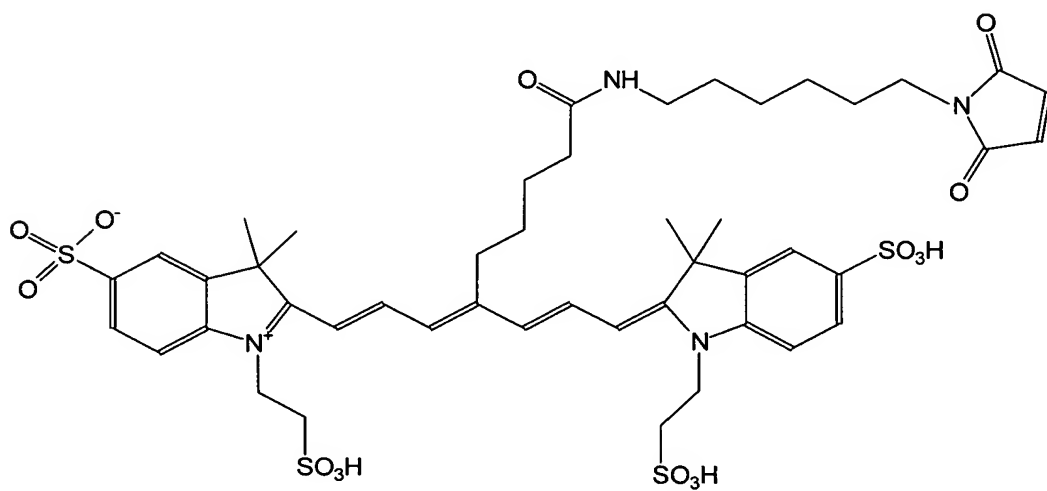
or of formula (III)



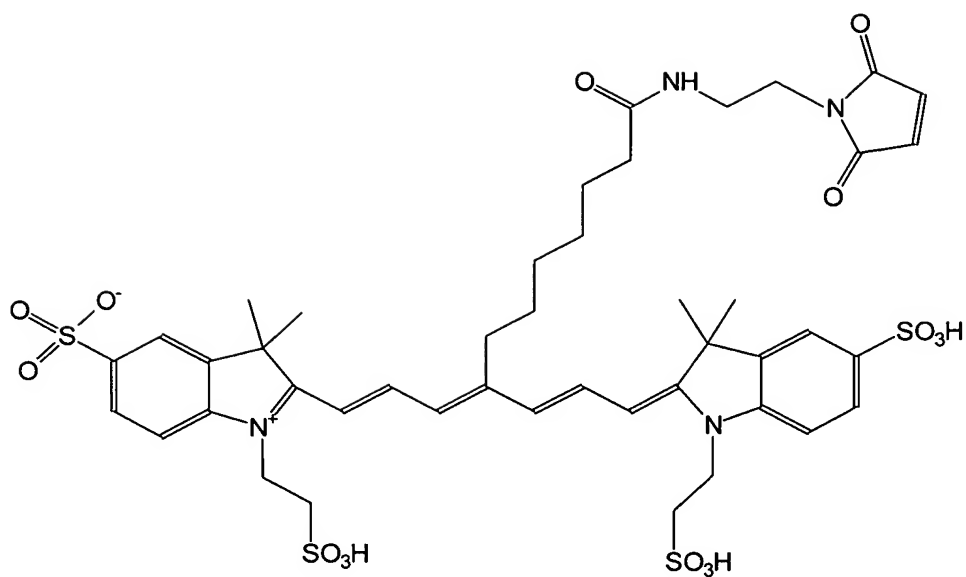
or of formula (V)



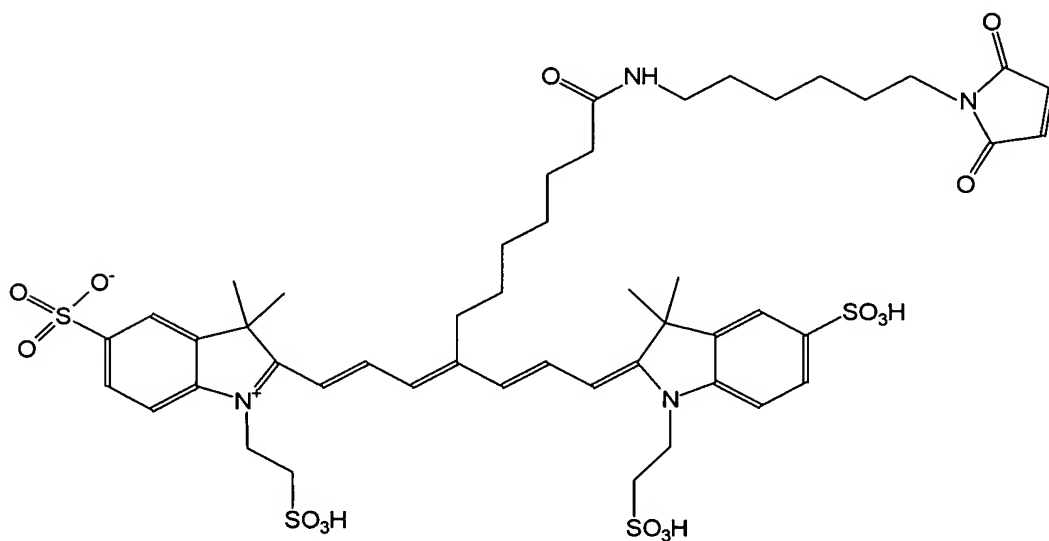
or of formula (VI)



or of formula (VIII)



or of formula (IX)



or a salt thereof.

41. A solvate of a compound of claim 40, which comprises a compound of formula II, III, V, VI, VIII or IX in combination with a solvent molecule.

(ix) EVIDENCE APPENDIX

None

(x) RELATED PROCEEDINGS APPENDIX

None